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Construction of Vicinal Tertiary and All-Carbon Quaternary Stereocenters via Ir-Catalyzed Regio-, Diastereo-, and Enantioselective Allylic Alkylation and Applications in Sequential Pd-Catalysis

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Abstract

Highly congested vicinal stereocenters comprised of tertiary and all-carbon quaternary centers were generated via Ir-catalyzed asymmetric allylic alkylation of β-ketoesters. These catalytic reactions proceed in excellent yields with a broad scope on either reaction partner, and with outstanding regio-, diastereo-, and enantiocontrol. Implementation of a subsequent Pd-catalyzed alkylation affords dialkylated products with pinpoint stereochemical control of both chiral centers.

The asymmetric construction of sterically encumbered vicinal stereogenic centers is of great interest to synthetic chemists due to the prevalence of such structural arrangements in natural products and bioactive compounds.[1] The limited number of methods that provide selective access to vicinal tertiary and all-carbon quaternary stereocenters highlights the challenging nature of this task. Enantioselective approaches for accessing this structural dyad have generally relied on asymmetric Michael additions[2] and Claisen rearrangements.[3] Among the methods available for forging this motif, only a relatively small number have been reported to do so by employing transition metals in a catalytic, asymmetric fashion.[4,5] Thus, further investigations into the development of metal-catalyzed methods to directly and selectively generate such stereochemical arrays should prove valuable.

Allylic alkylation chemistry represents a successful strategy for the assembly of highly congested chemical architectures[6] and, within this domain, Ir-catalyzed processes are among the most selective and highest yielding.[7,8] Initial reports from the Helmchen[9] and Hartwig[10] groups demonstrated the utility of Ir-catalyzed allylic substitutions for the synthesis of enantioenriched 3,3-disubstituted (branched) allyl compounds.[8] As this research area has developed, Ir/phosphoramidite catalysts (i.e. $[Ir(cod)Cl]_2$/**L1,** Figure 1)[11] have emerged as privileged scaffolds for the regio- and enantioselective allylic alkylation of achiral nucleophiles, such as malonate derivatives and ketone enolates.[12] However, methods for Ir-catalyzed intermolecular allylic alkylation that employ prochiral nucleophiles and display high (1) regio-, (2) diastereo-, and (3) enantioselectively remain elusive (Scheme 1).[13] To date, only two reports,[14] from the laboratories of Takemoto and Hartwig, detail success in attaining all three of these goals; however, in these accounts, the nucleophiles investigated were limited to amino acid derivatives and azlactones.[15] Herein, we report the development

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Supporting Information.
Experimental procedures, characterization data, single crystal X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

of a highly regio-, diastereo-, and enantioselective Ir-catalyzed α-allylic alkylation of cyclic β-ketoesters that forges vicinal tertiary and all-carbon quaternary centers in one step and in excellent yields. Moreover, we describe the deployment of a novel 2-(trimethylsilyl)-ethyl β-ketoester, which serves as an oxycarbonyl-protected enolate, enabling sequential catalyst-controlled α-allylic alkylations and, in turn, the ability to select the diastereomer produced within the nascent stereochemical dyad.

Our preliminary studies focused on probing the effects of different ligands, bases, additives, and solvents on the efficiency and selectivity of the reaction. Cyclic β-ketoester **1a**, cinnamyl carbonate **2a**, and $[Ir(cod)Cl]_2$/phosphoramidite complexes[16] were chosen as standard reaction components at the outset of our investigations.[17] Selected results of these experiments are summarized in Table 1.[18] Our investigations commenced with commonly used phosphoramidite ligand **L1**[19] and we were pleased to find that the proposed reaction proceeded smoothly under the conditions described (Table 1), delivering α-quaternary β-ketoester **3aa** in >95% conversion and in 96% ee. Unfortunately, no diastereoselectivity was observed in this case (Table 1, entry 1). Use of ligand **L2**, a diastereoisomer of **L1**, again produced a high yielding reaction, but in significantly diminished ee (32%) and modest 1:2 dr (entry 2). Inspired by the You group's use of Ir-*N*-arylphosphoramidite complexes (derived from $[Ir(cod)Cl]_2$ and **L3**)[20] to effect the diastereo- and enantioselective intramolecular allylation of indoles and pyrroles,[21] we envisioned that analogous Ir complexes may prove valuable for the generation of all-carbon quaternary stereocenters. We were delighted to discover that the use of *N*-aryl-phosphoramidite ligand **L3** furnished the desired product in 98% ee, >20:1 dr, and 95:5 branched to linear ratio (entry 3).

Extensive exploration of various bases, including organic and inorganic bases, revealed that the use of LiO*t*-Bu afforded the desired product in comparable selectivities as NaH (entries 4–8). Previous reports demonstrating the marked effect of LiCl over the regioselectivity[12b,12j,13b] in Ir-catalyzed allylic alkylations prompted us to investigate this and related additives. As a result of these efforts (entries 9–10), the combination of LiBr and THF, at 25 °C, was found to provide **3aa** in >20:1 dr, 95:5 branched:linear ratio, and with >99% ee (Table 1, entry 10).

Under these superior conditions, several more ligands were examined. Use of ligand **L4**[20b] afforded **3aa** in 96% ee and 12:1 dr (entry 11). Employment of *N*-aryl-phosphoramidite scaffolds proved critical to maintaining high diastereoselectivity in the reaction. Phosphinooxazoline (PHOX) type ligands (e.g. **L5**), first used in Ir-catalyzed allylation by Helmchen,[9] were also examined but we found these to be poorly suited for our reaction (entry 12). Finally, we found that the catalyst loading could be reduced to 1 mol % (entry 13) without loss of selectivity.

With optimized conditions in hand, the scope of substrates tolerated in the reaction was explored. We found that cinnamyl derived carbonates bearing either electron-donating (–OMe) or electron-withdrawing (–Br, $–CF_3$) groups on the aromatic ring gave remarkably high dr, ee and yields (99% ee and 20:1 dr, Table 2, entries 1–4). The branched to linear ratio (i.e., **3:4**) tended to decrease as the electron deficiency of the aryl substituents increased (from 95:5 to 71:29, with 4-OMe-C_6H_4 to 4-CF_3-C_6H_4, respectively, entries 2–4). Heteroaryl substituents, such as 3-pyridyl, 2-thienyl and 2-furanyl, were also installed with uniformly excellent enantioselectivities and high diastereoselectivities (95–98% ee and 10:1–17:1 dr, entries 5–7).

In addition to aromatic substituents, methyl sorbyl carbonate was also well tolerated in the chemistry providing diene **3ah**, although with a slight decrease in dr and ee (8:1 dr and 90% ee, entry 8).[22] Moreover, the reaction proceeded smoothly with ethyl β-ketoester **1b**,

providing the α-allyl β-ketoester **3ba** with excellent yield and selectivity (entry 9). Gratifyingly, aliphatic cyclic ketones also proved to be viable participants in the reaction. Cyclopentanone and cyclohexanone based substrates delivered the products **3ca** and **3da** in 98–99% ee and 8:1–20:1 dr, respectively (entries 10–11). Vinylogous ester, tetrahydropyran-4-one, and 4-piperidinone derivatives furnished the corresponding products (**3fa**–**3ha**) in high yields (85–99%), good diastereoselectivites (13:1–20:1), and enantioselectivities (97–99%, entries 13–15, Table 2). The absolute stereochemistry of the product **3af** (>99% ee) was determined as (*R*,*R*) by single-crystal X-ray analysis.[18]

During the course of our investigations we became intrigued by the possibility of developing a sequential allylic alkylation reaction, in which allylation of a dicarbonyl-stabilized enolate would be followed by decarboxylative allylic alkylation and, thus, engender the ability to select among all four possible stereochemical outcomes.[23,24] In order to realize such a consecutive allylic alkylation, we devised a novel oxycarbonyl-protected enolate, which we hypothesized would successfully undergo Ir-catalyzed allylic alkylation and be poised to subsequently participate in Pd catalysis. Specifically, we envisioned that treatment of 2-(trimethylsilyl)ethyl β-ketoester **5** with fluoride would trigger the release of fluorotrimethylsilane, ethylene, and CO_2 to reveal prochiral enolate **6** (Scheme 2). Enolate **6** could then be intercepted and engage in Pd-catalyzed allylic alkylation to deliver α-quaternary ketone **7**. In the case at hand, where β-ketoester **5** contains a chiral branched R group at the α position, we anticipated that with careful choice of catalyst, we could control the newly generated stereocenter independent of the absolute stereochemistry of the side chain.

We were pleased to find that 2-(trimethylsilyl)ethyl β-ketoester **1e** is a highly competent substrate for Ir-catalyzed allylic alkylation and, under standard conditions, gave the desired product (**3ea**) with excellent yield and selectivity (Table 2, entry 12). Moreover, exposure of **3ea** to catalytic $Pd_2(dba)_3$/**L6** (Table 3) in the presence of allyl methylcarbonate and tetrabutylammonium difluorotriphenylsilicate (TBAT) generated the desired diallylated α-quaternary ketone **8a** in good yield. The use of achiral PHOX ligand **L6** revealed that substrate **3ea** displays inherent selectivity under Pd catalysis, furnishing **8a**[25] as the major diastereomer (Table 3, entry 1). Use of (*S*)-*t*-BuPHOX ligand (*S*)-**L5** resulted in modest reversal of the inherent diastereoselectivity to generate **9a** predominantly (entry 2). Furthermore, we were interested to find that use of ligand (*S*)-**L7**, possessing both an electronically modified phosphine and a smaller *i*-Pr substituent on the oxazoline ring in contrast to the more standard *t*-Bu, produced **9a** with improved diastereoselectivity (**8a:9a**, 1:8 dr) and 91% yield (entry 3). Alternatively, through judicious choice of ligand (e.g., (*R*)-**L8**), the inherent selectivity of the system could be enhanced to afford **8a** with up to 18:1 dr (entries 4–5). Cursory investigation revealed that 2-aryl and 2-alkyl substitutions at the allyl-carbonate are well tolerated: allylic alkylation products **8b** and **8c** were obtained in good yields and with excellent diastereoselectivities.

In summary, a highly regio-, diastereo-, and enantio-selective method for the synthesis of vicinal tertiary and all-carbon quaternary centers was realized through the use of an $[Ir(cod)Cl]_2$/*N*-aryl-phosphoramidite (**L3**) catalyst system. Varied substitutions were well tolerated on both the β-ketoester and allyl carbonate fragments. A sequential Ir/Pd-catalyzed dialkylation protocol was also established to deliver bis-allylated α-quaternary ketones with excellent stereoselectivity, while affording access to either product diastereomer with catalyst control. Further studies exploring the mechanisms of these reactions and exploiting their applications in the total synthesis of complex natural products are underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. Methyl 2-oxocyclohexanecarboxylate was previously employed in Ir-catalyzed allylation with 95% ee and 1:1 dr, see ref 13b for detail.
18. See the Supporting Information for details.
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24. Attempts to establish a single-vessel diallylation protocol have, thus far, proved unsuccessful. Subjecting allyl 2-oxocyclohexanecarboxylate to the optimized reaction conditions resulted in nonstereoselective decarboxylative allylic alkylation. Sequential addition of all reaction components to substrate **3ea** also failed.
25. See SI for the determination of the relative configuration.[18]

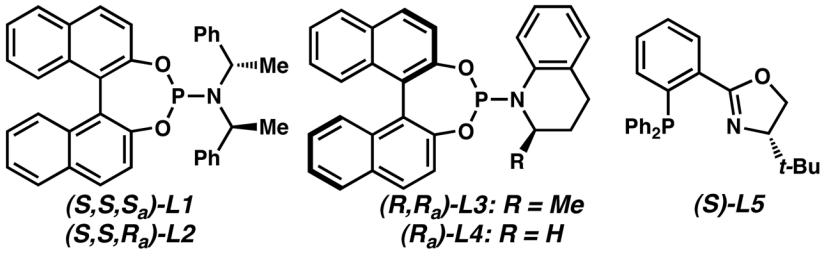
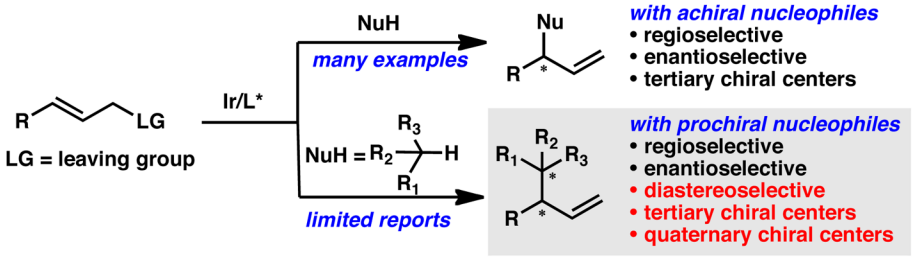
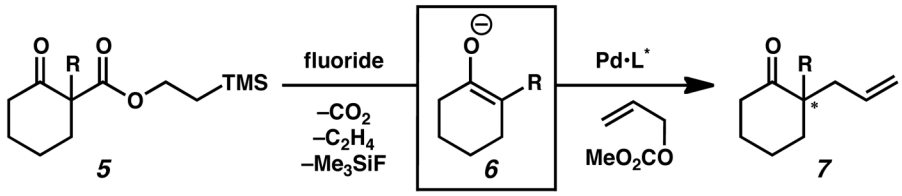


Figure 1.
Selected Phosphoramidite and PHOX Ligands.



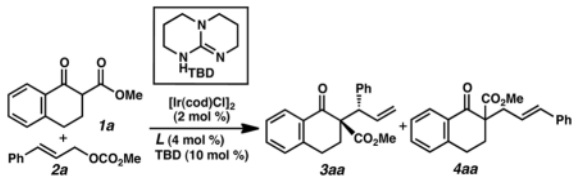
Scheme 1.
Ir-Catalyzed Allylic Substitutions.



Scheme 2.
Strategic Enolate Protection.

Table 1

Optimization of Reaction Parameters.[a]



entry	*L*	base or additive (equiv)	*3aa*:*4aa*[b]	dr of *3aa*[b]	ee of *3aa* (%)[c]
1	*L1*	NaH (2)	>95:5	1:1	96 (99)[d]
2	*L2*	NaH (2)	>95:5	1:2	32 (3)[e]
3	*L3*	NaH (2)	95:5	>20:1	98
4	*L3*	–	80:20	11:1	96
5	*L3*	Et_3N (2)	77:23	11:1	97
6	*L3*	Cs_2CO_3 (2)	63:37	6:1	93
7	*L3*	K_3PO_4 (2)	63:37	4:1	90
8	*L3*	LiO*t*-Bu (2)	95:5	>20:1	99
9	*L3*	LiCl (1)	88:12	14:1	98
10	*L3*	LiBr (1)	95:5	>20:1	>99
11	*L4*	LiBr (1)	80:20	12:1	96
12[f]	*L5*	LiBr (1)	12:88	–	–
13[g]	*L3*	LiBr (1)	95:5	>20:1	99

[a] Reactions performed with 0.1 mmol of **2a**, 0.2 mmol of **1a** at 0.1 M in THF at 20 °C and allowed to proceed to complete consumption of **2a**.

[b] Determined by ^{1}H NMR and UHPLC-MS analysis of the crude mixture.

[c] Determined by chiral HPLC analysis of the major diastereomer.

[d] (ee) of the alternate diastereomer.

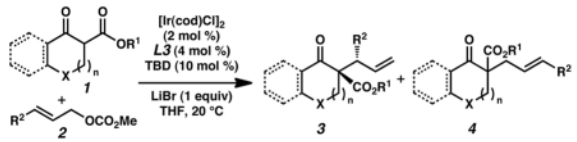
[e] (ee) of the major diastereomer.

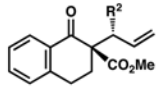
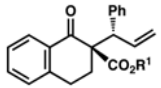
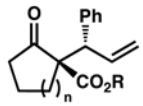
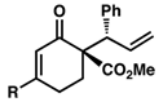
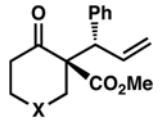
[f] Measured after 60 h at 60% conversion.

[g] 1 mol % $[Ir(cod)Cl]_2$ and 2 mol % **L3** were used.

Table 2

Substrate Scope of Ir-Catalyzed Allylic Alkylation of β-Ketoesters.[a]



entry	product (*3*)		*t* (h)	*3*:*4*[b]	dr of *3*[b]	yield (%)[c]	ee of *3* (%)[d]
1	 *3aa–3ah*	*3aa*: R^2 = Ph	1	95:5	>20:1	98	>99
2		*3ab*: R^2 = *p*-MeO-C_6H_4	1	95:5	20:1	99	>99
3		*3ac*: R^2 = *p*-Br-C_6H_4	8	90:10	>20:1	90	99
4		*3ad*: R^2 = *p*-CF_3-C_6H_4	12	71:29	>20:1	99	>99
5		*3ae*: R^2 = 3-pyridyl	12	50:50	11:1	98	98
6	 *3ba*	*3af*: R^2 = 2-thienyl	12	92:8	17:1	97	95
7		*3ag*: R^2 = 2-furanyl	12	95:5	10:1	90	95
8		*3ah*: R^2 = (*E*)-MeCH=CH	10	95:5	8:1	92	90
9		*3ba*: R^1 = Et	2	95:5	>20:1	98	>99
10		*3ca*: n = 1, R = Et	3	93:7	8:1	85	99
11		*3da*: n = 2, R = Et	12	90:10	20:1	88	98
12		*3ea*: n = 2 R = CH_2CH_2TMS	12	90:10	20:1	87	>99
13		*3fa*: R = O*i*-Bu	10	91:9	20:1	99	>99
14		*3ga*: X = O	10	90:10	16:1	88	98
15		*3ha*: X = NBn	12	85:15	13:1	85	97

[a]Reactions performed under the conditions of Table 1, entry 10.

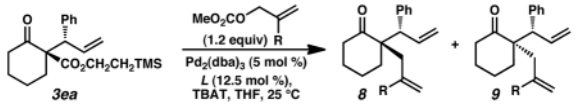
[b] Determined by ^{1}H NMR analysis of the crude mixture.

[c] Isolated yield of **3** and **4**.

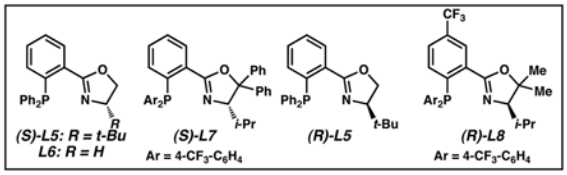
[d] Determined by chiral HPLC or SFC analysis of the major diastereomer.

Table 3

Development of Pd-Catalyzed Diastereoselective Decarboxylative Allylic Alkylation of TMSE-β-Ketoesters.[a]



entry	product (*8*/*9*)	ligand	%yield[b]	dr (*8*:*9*)[c]
1	*8*a/*9*a: R = H	*L6*	91	2:1
2	*8*a/*9*a: R = H	(*S*)-*L5*	79	1:2.2
3	*8*a/*9*a: R = H	(*S*)-*L7*[d]	91	1:8
4	*8*a/*9*a: R = H	(*R*)-*L5*	73	12:1
5	*8*a/*9*a: R = H	(*R*)-*L8*	85	18:1
6	*8*b/*9*b: R = Ph	(*R*)-*L8*	87	12:1
7	*8*c/*9*c: R = Me	(*R*)-*L8*	70	13:1



[a]Reactions performed with 1.2 equiv of TBAT, and 1.2 equiv of allyl methylcarbonate at 0.03 M.[18]

[b]Isolated yield of **8** and **9**.

[c]Determined by ^{1}H NMR analysis of the crude mixture and confirmed by GC analysis.

[d]10 mol % ligand was used.